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Application :	09/637962	**Examiner :**	Kemmerer	**GAU :**	1647
From:	Ihc	**Location:**	(IDC) FMF FDC	**Date:**	2/28/06
		Tracking #:	0605 1836	Week Date:	12/13/04

DOC CODE	DOC DATE	MISCELLANEOUS
☐ 1449		☐ Continuing Data
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☐ OATH		
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☒ SPEC		

[RUSH] **MESSAGE:** Table II on pages 36 and 37 of specs, has data cut off in last column. Please advise.

Thank you.

[XRUSH] **RESPONSE:**

Done

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DATE: 03/13/06 **FILE NUMBER:** ELX-5704(US); BXTR 9005
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PLEASE DELIVER THIS FACSIMILE TO: Rori Birch
THIS FACSIMILE IS BEING SENT BY: Kathleen M. Petrillo
NUMBER OF PAGES: 6 **INCLUDING COVER SHEET**

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Type of paper transmitted: Letter to Commissioner for Patents; Replacement Pages 37, 37a, 37b and 38

Applicant's Name: Lawrence H. Thompson

Serial No.: 09/637,962 **Examiner:** R. DeBerry

Filing Date: 08/11/00 **Art Unit:** 1647 **Confirmation No.:** 8001

Application Title: THERAPEUTIC METHODS FOR TREATING SUBJECTS WITH A RECOMBINANT ERYTHROPOIETIN HAVING HIGH ACTIVITY AND REDUCED SIDE EFFECTS

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March 13, 2006

Application of Lawrence H. Thompson
Serial No. 09/637,962
Filed August 11, 2000
Art Unit 1647
Confirmation No. 8001
For THERAPEUTIC METHODS FOR TREATING SUBJECTS WITH A RECOMBINANT ERYTHROPOIETIN HAVING HIGH ACTIVITY AND REDUCED SIDE EFFECTS
Attorney Docket No. ELX-5704(US); BXTR 9005

Re: Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Ms. Birch:

In response to our telephone conversation of Friday, March 10, 2006, enclosed are replacement pages 37, 37a, 37b and 38 which are intended to replace pages 37 and 38 of the original application.

Applicant believes these replacement pages now put the application in condition for issuance.

Respectfully submitted,

Kathleen M. Petrillo, Reg. No. 35,076

KMP/lam
*Enclosure

A fourth open, uncontrolled European trial included more than a 1000 HD patients. In total, 829 patients were evaluated for 26 weeks. Of these patients, 379 were administered Epoetin Omega by i.v. injection and 450 were administered by s.c. injection.

In a pilot study using an initial dose of 3x40 IU/kg/week, either i.v. or s.c., both hemoglobin and HCT rose quickly, leading to a reduction in the dose as early as after two weeks

Table II. Efficacy of i.v. epoetin omega in correcting renal anemia in HD patients. Summary of the results of 6 open, uncontrolled trials.

Trial (Reference)	Duration	No. of patients and dosing (IU/kg)	Iron	Baseline Hb (g/dL) and/or HCT (%)	Dose variations during trial	End point Hb and/or HCT	Other notices
India 1)	12 weeks	20, 3x25 i.v. 8 weeks, then 3x36	400 mg/day p.o. + Folic acid 5 mg/day	Hb 6.0±1.0 HCT 18.3±3	-	Hb 9.9±1.4 HCT 29.9±4.7	9/20 reached 10.0 g/dL Hb Continuous rise in Hb and HCT
India 2)	12 weeks	13, same as above	Iron dextran i.v. from 2. week on	Hb 6.1 (mean) HCT 18 (mean)	-	Hb 8.0 (mean) HCT 26 (mean)	Continuous rise in Hb and HCT
India 3)	12 weeks	15, same as above	Not stated	Hb 5.6±1.1 HCT 16.5±3.3	-	Hb 7.9±1.4 HCT 23.5±4.6	Continuous rise in Hb and HCT
India 4	12 weeks	22, same as above	150-300 mg/day p.o. + 200-300 mg/week i.v.	Hb 5.9±1.1 HCT 18.2±3.4	-	Hb 8.4±1.9 HCT 26±6	3/22 reached 10 g/dL Hb Continuous rise in Hb and HCT
Brazil	16 weeks	15, 3x50 i.v. (high dose, HD) 15, 3x25 i.v. (low dose, LD) Single dose ⇑ by 25 IU after week 4 if Hb rose ≤ 1.0 g/dL,	According to ferritin, i.v. or p.o., or without (ferritin >500 mg/mL)	HD: Hb 6.4 (mean) HCT 20 (mean) LD: Hb 7.0 (mean) HCT 22.5	HD group (IU/kg/wk) wk 1-6: 145-155 wk 7-12: 100-110 wk 12-16: 70-100	HD: Hb 10.4 (mean) HCT 32.2 (mean) LD: Hb 10.2 (mean) HCT 32.1 (mean)	Continuous rise in Hb and HCT in both dosage groups, but more rapid and prominent

		and during trial according to response. When Hb 10.0 g/dL, dose ⇓ by 1/3 – i.v. or s.c. (50%)		(mean)	<u>LD group (IU/kg/wk)</u> wk 1-4: 70-75 wk 5-13: 100-110 wk 14-16: 90-95		with the higher dose. HD group patients all reached 10.0 g/dL Hb. Time to target 7.4 ±2.7 weeks
Argentina	16 weeks	9, 3x25 i.v. 9, 3x50 i.v. Single dose ⇑ by 25 IU in 2-wk intervals, according to response in Hb	160 mg/day p.o. according to ferritin	Hb 5.7±1.0 HCT 17.0±3.2	<u>Overall average</u> wk 1-3: X=100-115 SD=30-36 wk 4-9: X=80-95 SD=20-45 wk 10-13: X=100-120 SD=50-60 wk 14-16: X=120-145 SD=55-60	Hb 8.9±1.1 HCT 26.7±3.2	Continuous rise in Hb and HCT regardless of the initial dose.

of treatment in majority of the patients. Accordingly, for the main part of the trial, initial doses of 3x30 IU/kg week i.v. or s.c. were used. Included patients had hemoglobin ≤9.0 g/dL, HCT ≤27%, and all standard inclusion/exclusion criteria for efficacy/safety trials of rHu EPOs.

The main objective of the trial was to increase and maintain hemoglobin at 10.0-12.0 g/dL, or at least to induce a rise in hemoglobin ≥2.0 g/dL and HCT >6% over the first 12 weeks of the trial. Dosing was divided in two periods: a titration period (needed to achieve the target) and a maintenance period (needed to keep hemoglobin and HCT within the target values with as little variability as possible). Dose adjustments were made every two weeks according to hemoglobin response and tolerability (single dose up or down by 5-20 IU/kg). Iron was supplemented orally or intravenously, depending on the iron status, so as to keep ferritin > 150 μg/L and transferrin saturation >20%. It is noted that in this study, patients were screened for the presence of EPO antibodies, and only two patients in the 1,000 showed presence of antibodies. Thus, the incidence of antibody formation with Epoetin Omega seems to be less than 0.2%.